

Characterization of Signet Ring Cell Carcinoma of the Stomach

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Background and Objectives: As there is no consensus regarding the prognosis of patients with signet cell carcinoma of the stomach compared with other types of gastric cancer, we retrospectively studied the clinicopathologic features and prognosis of signet cell carcinoma in comparison with other types of gastric cancer.

Methods: Gastrectomies were performed because of gastric cancer in 1,498 patients between 1970 and 1994. Of the 154 patients diagnosed with signet ring cell carcinoma, 94 had early and 60 had advanced gastric carcinoma. The percentage of patients with an early carcinoma was significantly higher among those with signet ring cell carcinoma compared with those with other gastric carcinoma histologies.

Results: The survival of the total group of patients with signet ring cell carcinoma was significantly better than that of patients with other types of gastric carcinoma ($P < 0.05$). Survival of the subset of patients with early signet ring cell carcinoma was also improved compared with patients with other types of gastric carcinoma ($P < 0.05$). However, patients with advanced signet ring cell carcinoma had a poor prognosis similar to that of patients with other types of gastric carcinoma.

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KEY WORDS: gastric carcinoma; survival rate; early gastric cancer; advanced gastric cancer

INTRODUCTION

Signet ring cell carcinomas, characterized by their poor prognosis and potential to infiltrate the gastric wall [1,2], have been variously designated as diffuse type by Lauren [1], infiltrative type by Ming [3], or undifferentiated type by Sugano et al. [4]. Antonioli and Goldman have reported that 29% of patients with gastric cancer had a signet ring cell type histology [5]. Signet ring cell carcinoma of the stomach appears to occur at a higher frequency in females and young patients [5]. The postoperative survival of patients with signet ring cell carcinoma of the stomach has been analyzed and compared with that of patients with other histologies. Kim et al. have reported no significant difference 5-year survival rates between patients with signet ring cell type and other early stage gastric carcinoma types, although the prognosis for patients with advanced signet ring cell type was

significantly worse than for patients with other types of advanced gastric carcinoma [6]. In contrast, Maehara et al. have reported that patients with signet ring cell carcinoma can expect a longer survival than those with other cell types of gastric carcinoma [7]. Thus, there is no consensus regarding the prognosis of patients with signet ring cell gastric carcinoma.

In this paper we describe the clinicopathologic features and prognosis of patients with signet ring cell carcinoma of the stomach compared with other gastric carcinoma types.

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TABLE I. Clinicopathologic Findings in Patients With Signet Ring Cell Carcinoma and Other Types of Gastric Carcinoma[†]

	Signet ring cell carcinoma (n = 154)	Other types of gastric carcinoma (n = 1,344)	P value
Age (years, mean)	55.6	60.2	NS
Gender (female/male)	70/84	438/906	<0.05*
Tumor size (cm, mean)	5.1	5.3	NS
Primary tumor (T1/T2/T3/T4)	94/30/24/6	474/319/436/115	<0.05*
Location (upper/middle/lower/whole)	71/54/14/15	481/535/234/94	<0.05*
Regional lymph nodes (positive/negative)	43/111	674/670	<0.05*
Liver metastasis (positive/negative)	2/152	72/1272	<0.05*
Peritoneal metastasis (positive/negative)	15/139	124/1220	NS
Cancer stage (I/II/III/IV)	110/10/16/18	602/154/315/273	<0.05*
Curability (A/B/C)	115/25/14	663/449/232	<0.05*
Lymph node dissection (D0/D1/D2/D3/D4)	1/30/102/7/14	36/253/899/49/107	NS

[†]NS, not significant; D0, no lymph node dissection; D1, dissection of N1 lymph nodes; D2, dissection of N1 and N2 lymph nodes; D3, dissection of N1, N2, and N3 lymph nodes; D4, dissection of N1, N2, N3, and N4 lymph nodes; Curability A, no residual tumors with high probability of cure; Curability B, no residual tumors but not evaluable as "Curative A"; Curative C, definite residual tumors.

*Significant difference.

MATERIALS AND METHODS

Patients

Members of the First Department of Surgery, Kyoto Prefectural University of Medicine, Japan, performed gastric resections for carcinoma in 1,498 patients between 1970 and 1994. Signet ring cell carcinoma was demonstrated in 154 (10.3%) patients. Of the patients with signet ring cell carcinoma, 94 of 154 (61.0%) had early gastric carcinomas, and 60 (39.0%) had advanced gastric carcinomas. The diagnosis of signet ring cell carcinoma was made if an adenocarcinoma with a predominant component (>50%) of isolated tumor cells containing mucin was seen [8]. Pathologic diagnoses and classification were based on the Japanese Classification of Gastric Carcinoma [9]. All of the tissues were examined by pathologists.

Surgical Technique

The surgical procedures were performed by attending surgeons or by surgical fellows under their supervision. Patients with gastric carcinoma located in the upper middle or proximal portion of the stomach underwent total gastrectomy, and those with gastric carcinomas located in the lower middle or distal portion of the stomach underwent distal gastrectomy by the same technique. The tumors were graded according to the Japanese Classification of Gastric Carcinoma [9].

Statistical Analysis

Statistical analysis used the *NAP* system (version 4.0) [10]. The first objective of the statistical analysis was to compare the clinicopathologic characteristics of signet ring cell carcinoma and the other types of gastric carcinoma. Information collected from the medical records included age and gender of the patients, size, location, gross appearance and depth of invasion of the primary

tumor, the presence of regional lymph node involvement, liver and peritoneal metastasis, and the level of lymph node dissection. The cancer stage and status of curability also were recorded. The clinicopathologic findings in patients with signet ring cell carcinoma and other types of carcinoma were also stratified according to early or advanced gastric carcinoma.

The second objective of the statistical analysis was to compare postoperative survival between the patients with signet ring cell carcinoma and the other types of gastric carcinoma. The Kaplan-Meier method and generalized Wilcoxon test were used.

RESULTS

Clinicopathologic Findings

Significant differences were noted in patient gender, depth of invasion, location of the primary tumor, prevalence of liver and regional lymph node metastases, and tumor stage and curability between patients with signet ring cell carcinoma and other types of gastric carcinoma (Table I). Patients with early signet ring cell carcinoma tended to be female. In terms of the gross appearance, more IIc and less I or IIa type early cancers were observed in the patients with signet ring cell carcinoma. More early signet ring cell carcinoma tended to be located in the middle stomach than other types of early carcinoma (Table II). Tumors were larger and peritoneal metastasis more frequent in patients with advanced signet ring cell carcinoma. More patients with signet ring cell carcinoma underwent extended radical lymph node dissection and curative surgery (Table III).

Survival Rate

The postoperative cumulative 10-year survival of patients with signet ring cell carcinoma of the stomach was 68.2% compared with 43.9% for patients with other types of gastric carcinoma. This difference was statistically significant ($P < 0.05$) (Fig. 1). Postoperative sur-

TABLE II. Clinicopathologic Findings in Patients With Early Signet Ring Cell Carcinoma and Other Types of Early Gastric Carcinoma[†]

	Signet ring cell carcinoma (n = 94)	Other types of gastric carcinoma (n = 474)	P value
Age (years, mean)	54.8	59.9	NS
Gender (female/male)	42/52	132/342	<0.05*
Tumor size (cm, mean)	3.1	2.8	NS
Gross appearance (I/IIa/IIb/IIc/III/other)	1/8/3/77/0/5	32/112/11/274/10/35	<0.05*
Location (upper/middle/lower/whole)	4/53/36/1	48/223/203/0	<0.05*
Regional lymph nodes (positive/negative)	5/89	39/435	NS
Liver metastasis (positive/negative)	1/93	1/473	NS
Peritoneal metastasis (positive/negative)	0/94	1/473	NS
Cancer stage (I/II/III/IV)	92/2/0/0	464/7/1/2	NS
Curability (A/B/C)	91/1/2	453/18/3	NS
Lymph node dissection (D0/D1/D2/D3/D4)	1/24/68/1/0	4/125/332/6/7	NS

[†]NS, not significant; D0, no lymph node dissection; D1, dissection of N1 lymph nodes; D2, dissection of N1 and N2 lymph nodes; D3, dissection of N1, N2, and N3 lymph nodes; D4, dissection of N1, N2, N3, and N4 lymph nodes; Curability A, no residual tumors with high probability of cure; Curability B, no residual tumors but not evaluable as "Curative A"; Curative C, definite residual tumors.

*Significant difference.

TABLE III. Clinicopathologic Findings in Patients With Advanced Signet Ring Cell Carcinoma and Other Types of Advanced Carcinoma[†]

	Signet ring cell carcinoma (n = 60)	Other types of gastric carcinoma (n = 870)	P value
Age (years, mean)	56.8	60.3	NS
Gender (female/male)	28/32	306/564	NS
Tumor size (cm, mean)	8.3	6.6	<0.05*
Gross appearance (I/II/III/IV/other)	1/7/19/20/13	25/235/392/125/93	NS
Location (upper/middle/lower/whole)	18/18/10/14	258/332/186/94	NS
Regional lymph nodes (positive/negative)	38/22	635/235	NS
Liver metastasis (positive/negative)	1/59	71/799	NS
Peritoneal metastasis (positive/negative)	15/45	123/747	<0.05*
Cancer stage (I/II/III/IV)	18/8/16/18	138/147/314/271	NS
Curability (A/B/C)	24/24/12	210/431/229	<0.05*
Lymph node dissection (D0/D1/D2/D3/D4)	0/6/34/6/14	32/128/567/43/100	<0.05*

[†]NS, not significant; D0, no lymph node dissection; D1, dissection of N1 lymph nodes; D2, dissection of N1 and N2 lymph nodes; D3, dissection of N1, N2, and N3 lymph nodes; D4, dissection of N1, N2, N3, and N4 lymph nodes; Curability A, no residual tumors with high probability of cure; Curability B, no residual tumors but not evaluable as "Curative A"; Curative C, definite residual tumors.

*Significant difference.

vival was also examined as a function of patient stage (early or advanced cancer) because signet ring cell carcinomas were more often early gastric carcinomas. The cumulative 10-year survival for patients with early signet ring cell carcinoma was 93.0% compared with 76.3% for patients with other types of early gastric carcinoma. ($P < 0.05$) (Fig. 2). The cumulative 10-year survival for patients with advanced signet ring cell carcinoma was 44.4% compared with 27.5% for patients with other types of advanced gastric carcinoma. This did not represent a significant difference (Fig. 3).

DISCUSSION

The incidence of signet ring cell gastric carcinoma is lower in Japan than in Western countries. Maehara et al. have reported that 51 of 1,500 Japanese patients (3.4%)

with gastric carcinoma who had resections had signet ring cell carcinoma [7]. In contrast, Antonioli et al. have reported that 29% of their patients had signet ring cell gastric carcinoma [5]. In the present study signet ring cell carcinoma made up 10.3% of the total cases. The male/female ratio of patients with signet ring cell carcinoma in this study was 1.2:1, in contrast to the 2.1:1 ratio for other types of gastric carcinoma. The proportion of female patients with signet ring cell carcinoma in our study was higher than has been reported in the literature. Signet ring cell carcinomas in our study were observed more frequently in the middle stomach and less frequently in the upper third of the stomach than to other types of gastric carcinomas.

In the present study clinicopathologic findings and postoperative survival were also examined as a function

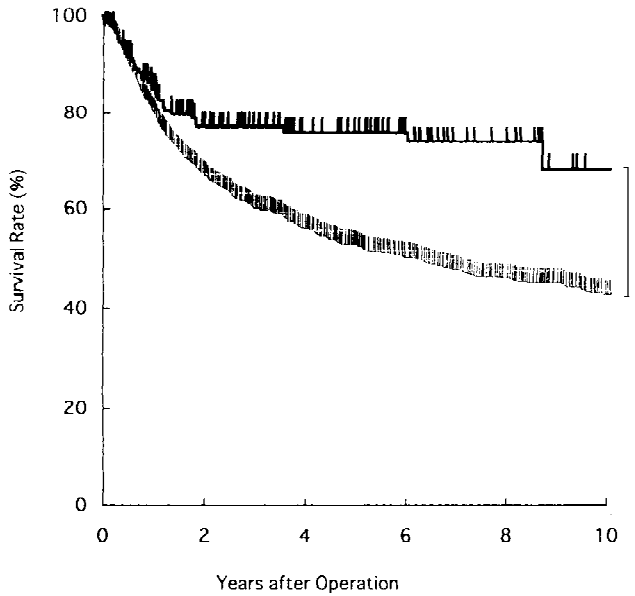


Fig. 1. The postoperative cumulative 10-year survival of patients who underwent gastrectomy for gastric cancer. The survival of the patients with signet ring cell carcinoma was significantly better than that of the patients with other types of gastric carcinoma ($P < 0.05$). Heavy line, signet ring cell carcinoma; thin line, other types of carcinoma; *, significant difference.

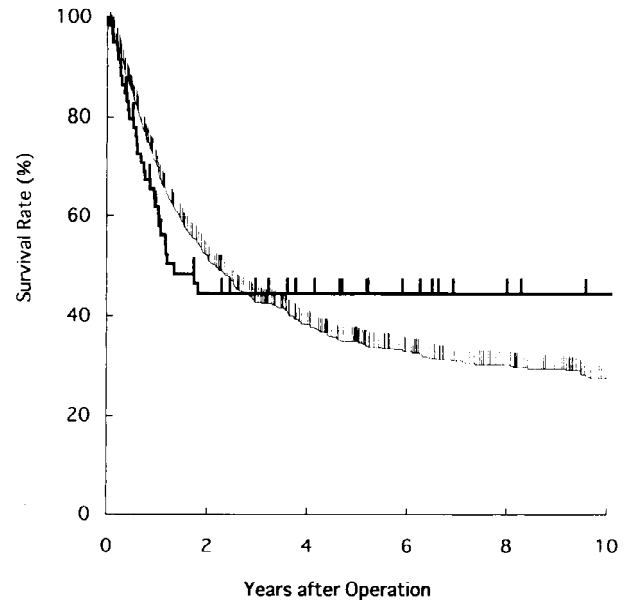


Fig. 3. The postoperative cumulative 10-year survival of patients who underwent gastrectomy for advanced gastric cancer. There were no significant difference between patients with advanced signet ring cell carcinoma and other types of advanced gastric carcinoma. Heavy line, signet ring cell carcinoma; thin line, other types of carcinoma.

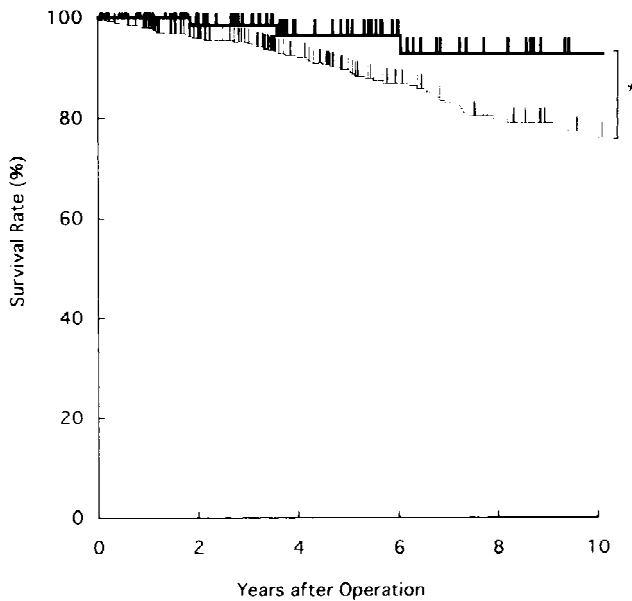


Fig. 2. The postoperative cumulative 10-year survival of patients who underwent gastrectomy for early gastric cancer. The survival of patients with early signet ring cell carcinoma was significantly better than that of the patients with other types of early gastric carcinoma ($P < 0.05$). Heavy line, signet ring cell carcinoma; thin line, other types of carcinoma; *, significant difference.

of patient stage (early or advanced cancer). Among patients with early gastric carcinomas, signet ring cell carcinomas were more often depressed and less often elevated. Advanced signet ring cell carcinomas were more often associated with peritoneal metastasis.

Kim et al. have reported [6] that the survival of patients with early signet ring cell carcinoma was not significantly different from that of patients with other types of early gastric carcinoma. In contrast, the survival of patients with early signet ring cell carcinoma in the present study was significantly better than that of patients with other types of early gastric carcinoma. Kim et al. have also reported a worse prognosis for patients with advanced signet ring cell carcinoma, especially stage III [6], while no significant difference was seen among the types of advanced gastric carcinoma in the present study. The results of Maehara et al. [7], were similar to the present study as patients with signet ring cell carcinoma had a better survival rate than patients with other cell types. Although Kim et al. commented that their results can be explained by the higher proportion of early carcinomas among their signet ring cell type carcinoma patients, better postoperative survival in their patients with early signet ring cell carcinoma was significantly better than in patients with other types of early carcinoma.

Because the lesions of early signet ring cell gastric carcinoma tend to be depressed, gastroendoscopic detection often uses contrast with indigo carmine solution. Moreover, the carcinoma cells are detected easily in biopsy specimens because of their typical enriched intracytoplasmic mucin and peripheral compressed nuclei. Consequently, signet ring cell gastric carcinoma can be detected at an early stage. Although it rarely involves the entire stomach and seldom invades the gastric wall, peritoneal metastasis often occurs and the prognosis is poor once signet ring cell carcinoma has become advanced.

In conclusion, we found that signet ring cell carcinoma could be detected at an early stage and that the prognosis of patients with early signet ring cell carcinoma was better than that of patients with other types of early gastric carcinoma. However, advanced signet ring cell gastric carcinoma had a typically poor prognosis similar to other types of gastric carcinoma.

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